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(54) CONTRACEPTIVE PREPARATIONS

(71) We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with contraceptive preparations.

Hormonal methods of contraception have been known, for example the oral administration of Enovid, Ovulen and Anovlar (Registered Trade Marks) and similar combinations of oestrogenic and gestagenic active principles. Experiments have also been made with corresponding preparations for administration by injection in which the active components provide a depot from which they are slowly liberated.

The disadvantage of the latter method is, in particular, the unpredictability of onset, the duration and the extent of withdrawal bleeding. The published experiments (see, for example, B. Czernobilsky et al., Fertil. and Steril, 20, 1; 75—90 [1969]), in which a prolonged-action oestrogen and a prolonged-action gestagen are administered together in the first week of the menstrual cycle by injection to suppress ovulation by means of an adequately high oestrogen and progesterone level, have shown that the reduction of the progesterone concentration in the body is not uniform enough to enable the onset of withdrawal bleeding to be predicted within a span of a few days, which is generally possible in the case of natural menstruation.

The disadvantage of oral administration lies in the fact that a tablet has to be taken daily, which means a comparatively high intake of hormones. This gives rise to undesirable side-effects, for example vomiting, increase in weight and so forth.

The present invention is based on the discovery of a new method of contraception in which the combination of a gestation, in a comparatively small dose, and an oestrogen is administered after the 10th day, preferably in the second half, of the menstruation cycle.

Accordingly, the present invention provides a contraceptive preparation suitable for parenteral administration or administration by implantation, which comprises, in unit dosage form, from 0.5 to 100 mg of a gestagen in admixture or conjunction with from 0.5 to 500 mg of an oestrogen.

The contraceptive preparations of the present invention may be administered, preferably in the form of oily solutions, parenterally, preferably intramuscularly or subcutaneously. However, it is also possible to administer the preparations by implantation.

It is further possible to administer the oestrogen and the gestation singly. Accordingly, the present invention also provides a contraceptive preparation which is made up in two parts ready for administration, the one part comprising, in unit dosage form, from 0.5 to 500 mg of an oestrogen and the other part comprising, in unit dosage from, from 0.5 to 100 mg of a gestation.

In the new contraceptive method using the preparations of the present invention the comparatively small dose of the gestagen ensures reliable onset of withdrawal bleeding, that is to say, predictable within a span of a few days, as in natural menstruation, and the simultaneous injection of a depot-oestrogen inhibits ovolution and/or nidation in at least the following menstruation cycle by change within the female reproductive system.

Furthermore, the contraceptive action can be determined for a given period of time by appropriate variation of the concentration of active principles. When using a preparation of the present invention it is possible, by a single administration of the preparation, to prevent conception for a period covering one or more menstrual cycles, that is to say for a period of from approximately four weeks to six months or even longer, it being possible to bring about withdrawal bleeding within a few days after administration, without termination of the contraceptive action, by the additional paren-

[*Price 5s. 0d. (25p)*]

teral or even oral administration of a gestagen.

As has already been stated, the oestrogenic and gestagenic components are preferably administered together. For this purpose the active principles are dissolved in one of the solvents known to be suitable for parenteral injection, with which a man skilled in the art will be familiar, filtered under sterile conditions and introduced into ampoules under aseptic conditions. Preference is given to oily solvents, for example sesame oil or castor oil. A diluent or a solubilizer, for example benzyl benzoate, may be added to the oil solutions to increase the solubility of the active principles.

In addition to the above-mentioned solvents, it is also possible to use vegetable oils, for example linseed oil, cottonseed oil, sunflower oil, peanut oil, olive oil and wheat oil. Also suitable are synthetic solvents, for example glycol, lactic acid esters and benzyl alcohol. Naturally, the selection of solvents given above is by no means complete. It is not necessary to provide a complete list, because a man skilled in the art will know which of the known solvents to choose for a specific purpose.

It is generally preferable to administer the contraceptive preparation at four-week intervals to imitiate the regular menstrual cycle. If the interval between administration is prolonged, for example, to several months, either on the advice of a physician or at the patient's request, only one withdrawal bleeding takes place, with complete contraceptive protection, during the interval between times of administration, unless additional gestation is given.

As the oestrogenic component of the preparations of the invention there is advantageously used an oestrogen having a protracted active life of at least 14 days. The oestrogen used is preferably administered in such doses and at such intervals that the suppression of ovulation achieved with the preparations of the present invention is at least equal to that achieved with a daily oral administration of 0.05 mg of ethynyl-oestradiol. Furthermore, the oestrogen used is preferably of the kind that produces a longer period of ovulation inhibition than is produced by such a dose of orally administered ethynyl-oestradiol. Preferred oestrogen components are, in particular, oestradiol esters, for example oestradiol oenanthate, oestradiol undecylate, oestradiol palmitate, oestradiol butyrate and oestradiol benzoate.

The decision as to which oestrogen is the most suitable active principle to use in the preparations depends largely on the desired period of contraceptive protection. If the protective action is to cover only one menstrual cycle, in other words about four weeks, it may be quite adequate to administer oestradiol valerate, which, as is known, is liberated from a depot for only a comparatively short period.

The contraceptive preparations of the present invention suitable for parenteral administration or administration by implantation are, like the two-part preparations of the present invention, in unit dosage form. The amount of oestrogen in the unit dosage form preparations is within the range of from 0.5 to 500 mg. per unit dose. The choice of oestrogen is advantageously such that a dose of preferably 5 to 50 mg, per unit dose, is sufficient to ensure the successful use of the preparations of the present invention.

When using oestradiol oenanthate to give contraceptive protection for a period of one menstrual cycle (about four weeks), a dose of 10 mg is generally sufficient. If the period of contraception is to be prolonged and the preferred dosage limit of 50 mg has to be exceeded, the oestrogen component may be increased to 250 mg.

Substances suitable for use as the gestation component in the preparations of the present invention are all those which, when administered in a comparatively small dose in accordance with the present invention, bring about predictable withdrawal bleeding similar in intensity and duration to normal menstruation. Preferred gestagens are those having a medium or long period of activity. The preferred concentration in the unit dosage form preparations is within the range of from 10 to 100 mg, especially 10 to 50 mg. A concentration within the range of from 0.5 to 50 mg, per unit dose, is adequate in the case of the highly active gestations. As examples of gestagens that may be used in the preparations of the present invention there may be mentioned: progesterone and the physiologically tolerable 3-enolesters thereof, hydroxy - progesterone - caproate, hydroxy - nor - progesterone - caproate, medroxy - proges - terone - acetate, nor - ethyndrone caproate and 17α - ethynyl - 18 - homo - 19 - nor - testosterone. Also suitable are 17α - hydroxy - progesterone derivatives, for example 17α - hydroxy - 19 - nor - progesterone, 6α - methyl - 17α - hydroxy - progesterone, 6 - methyl - 6 - dehydro - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 16α - methyl - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16α - methyl - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16β - methyl - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 16β - methyl - 17α - hydroxy - progesterone, 6, 16 - dimethyl - 6 - dehydro - 17α - hydroxy - progesterone, 6 - methyl - 6 - dehydro - 16 - methylene - 17α - hydroxy progesterone, 6 - chloro - 6 - dehydro - 16 - methylene - 17α - hydroxy - progesterone, 1, 2 - methylene - 6 - chloro - 6 - dehydro -

17α - hydroxyprogesterone, 1, 2 - methylene - 6 - fluoro - 6 - dehydro - 17α - hydroxy - progesterone, 17α - ethynyl - testosterone, 17α - ethynyl - 19 - nor - testosterone, 17α - ethynyl - $\Delta^{5(10)}$ - oestren - 17β - ol - 3 - one, 17α - methyl - 19 - nor - testosterone, 17α - ethynyl - Δ^4 - oestrene - 3β, 17β - diol, 17α - ethynyl - Δ^4 - oestren - 17β - ol, 17α - alkyl - Δ^4 - oestren - 17β - ols and the physiologically tolerable straight-chain or branched chain esters thereof, for example acetates, valerates, butyrates, caproates, oenanthates and undecylates. The ester group may be substituted in the usual manner, for example, by one or more substituents selected from halogen atoms and hydroxyl, carbonyl, keto and amino.

The contraceptive preparations of the present invention may, if desired, be used to prevent conception in domestic animals. Accordingly, the present invention further provides a method of treating a domestic animal, wherein there is administered to a domestic animal 0.5 to 500 mg of an oestrogen and 0.5 to 100 mg of a gestagen.

EXAMPLE

A contraceptive preparation in the form of an oily solution was prepared in the following manner.

A mixture of 15 grams of oestradiol oenanthate and 5 grams of 17α - hydroxy - progesterone caproate were made up to 1000 millilitres with a 6:4 mixture of castor oil/benzyl benzoate. The resulting solution was sterilized in the usual manner and introduced into 1 millilitre ampoules under aseptic conditions.

WHAT WE CLAIM IS:—

1. A contraceptive preparation suitable for parenteral administration or administration by implantation, which comprises, in unit dosage form, from 0.5 to 100 mg of a gestagen in admixture or conjunction with from 0.5 to 500 mg of an oestrogen.

2. A contraceptive preparation as claimed in claim 1, which is in a form suitable for subcutaneous or intramuscular injection.

3. A contraceptive preparation as claimed in claim 1 or 2, which is in the form of an oily solution.

4. A contraceptive preparation as claimed in claim 3, containing sesame oil or castor oil as solvent.

5. A contraceptive preparation as claimed in claim 3 or 4, wherein the preparation also contains a diluent or a solubilizer.

6. A contraceptive preparation as claimed in claim 5, wherein the diluent or solubilizer is benzyl benzoate.

7. A contraceptive preparation as claimed in claim 3, containing a mixture of castor oil and benzyl benzoate as solvent.

8. A contraceptive preparation as claimed in any one of claims 1 to 7, which contains from 5 to 50 mg of the oestrogen and from 10 to 50 mg of the gestagen.

9. A contraceptive preparation as claimed in any one of claims 1 to 8, wherein the oestrogen is oestradiol oenanthate, oestradiol undecylate, oestradiol palmitate, oestradiol butyrate or oestradiol benzoate.

10. A contraceptive preparation as claimed in any one of claims 1 to 9, wherein the gestagen is hydroxy - progesterone caproate, hydroxy - nor - progesterone caproate, medroxy-progesterone acetate or nor-ethyndrone caproate.

11. A contraceptive preparation as claimed in any one of claims 1 to 9, wherein the gestagen is 17α - hydroxy - 19 - nor - progesterone, 6α - methyl - 17α - hydroxy - progesterone, 6 - methyl - 6 - dehydro - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 16α - methyl - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16α - methyl - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16β - methyl - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 16β - methyl - 17α - hydroxy - progesterone, 6, 16 - dimethyl - 6 - dehydro - 17α - hydroxy - progesterone, 6 - methyl - 6 - dehydro - 16 - methylene - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16 - methylene - 17α - hydroxy - progesterone, 1, 2 - methylene - 6 - chloro - 6 - dehydro - 17α - hydroxy - progesterone, 1, 2 - methylene - 6 - fluoro - 6 - dehydro - 17α - hydroxy - progesterone, 17α - ethynyl - testosterone, 17α - ethynyl - 19 - nor - testosterone, 17α - ethynyl - $\Delta^{5(10)}$ - oestren - 17β - ol - 3 - one, 17α - methyl - 19 - nor - testosterone, 17α - ethynyl - Δ^4 - oestrene - 3β, 17β - diol, 17α - ethynyl - Δ^4 - oestren - 17β - ol or a 17α - alkyl - Δ^4 - oestren - 17β - ol or a physiologically tolerable ester thereof.

12. A contraceptive preparation as claimed in claim 11, wherein the ester is an acetate, valerate, butyrate, caproate, oenanthate or undecylate.

13. A contraceptive preparation as claimed in any of claims 1 to 9, wherein the gestagen is progesterone or a physiologically tolerable 3-enolester thereof.

14. A contraceptive preparation as claimed in any one of claims 1 to 9, wherein the gestagen is 17α - ethynyl - 18 - homo - 19 - nor - testosterone.

15. A contraceptive preparation suitable for parenteral administration or administration by implantation, which is made up in two parts ready for administration, the one part comprising in unit dosage form from 0.5 to 500 mg of an oestrogen and the other part com-

prising in unit dosage form from 0.5 to 100 mg of a gestagen.

16. A contraceptive preparation as claimed in claim 15, wherein the part comprising an oestrogen is in a form suitable for parenteral administration.

17. A contraceptive preparation as claimed in claim 16, wherein the part comprising an oestrogen is in a form suitable for subcutaneous or intramuscular injection.

18. A contraceptive preparation as claimed in claim 15, wherein the part comprising an oestrogen is in a form suitable for administration by implantation.

19. A contraceptive preparation as claimed in any one of claims 15 to 18, wherein one of or each of the parts is in the form of an oily solution.

20. A contraceptive preparation as claimed in any one of claims 15 to 19, wherein the oily solution contains sesame oil or castor oil as solvent.

21. A contraceptive preparation as claimed in claim 20, wherein the oily solution also contains benzyl benzoate.

22. A contraceptive preparation as claimed in any one of claims 15 to 21, containing 10 to 50 mg of the gestagen.

23. A contraceptive preparation as claimed in any one of claims 15 to 22, containing 5 to 50 mg of the oestrogen.

24. A contraceptive preparation as claimed in any one of claims 15 to 23, wherein the oestrogen is oestradiol oenanthate, oestradiol undecylate, oestradiol palmitate, oestradiol butyrate or oestradiol benzoate.

25. A contraceptive preparation as claimed in any one of claims 15 to 24, wherein the gestagen is hydroxy - progesterone caproate, hydroxy - nor - progesterone caproate, medroxy - progesterone acetate or nor-ethyndrone caproate.

26. A contraceptive preparation as claimed in any one of claims 15 to 24, wherein the gestagen is 17α - hydroxy - 19 - nor - progesterone, 6α - methyl - 17α - hydroxy - progesterone, 6 - methyl - 6 - dehydro - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 16α - methyl - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16α - methyl - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16β - methyl - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 16β - methyl - 17α - hydroxy - progesterone, 6, 16 - dimethyl - 6 - dehydro - 17α - hydroxy - progesterone, 6 - methyl - 6 - dehydro - 16 - methylene - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16 - methylene - 17α - hydroxy - progesterone, 1, 2 - methylene - 6 - chloro - 6 - dehydro - 17α - hydroxy - progesterone, 1, 2 - methylene - 6 - fluoro - 6 - dehydro - 17α - hydroxy - progesterone, 17α - ethynyl - testosterone, 17α - ethynyl - 19 - nor - testosterone, 17α - ethynyl - $\Delta^{5(10)}$ - oestren - 17β - ol - 3 - one, 17α - methyl - 19 - nor - testosterone, 17α - ethynyl - Δ^4 - oestrene - 3β, 17β - diol, 17α - ethynyl - Δ^4 - oestren - 17β - ol or a 17α - alkyl - Δ^4 - oestren - 17β - ol or a physiologically tolerable straight-chain or branched chain ester thereof.

27. A contraceptive preparation as claimed in claim 26, wherein the ester is an acetate, valerate, butyrate, caproate, oenanthate or undecylate.

28. A contraceptive preparation as claimed in any one of claims 15 to 24, wherein the gestagen is progesterone or a physiogically tolerable 3-enolester thereof.

29. A contraceptive preparation as claimed in any one of claims 15 to 24, wherein the gestagen is 17α - ethynyl - 18 - homo - 19 - nor - testosterone.

30. A contraceptive preparation having a composition substantially as described in the Example herein.

31. A contraceptive method of treating a domestic animal, wherein from 0.5 to 500 mg of an oestrogen and from 0.5 to 100 mg of a gestagen are administered parenterally or by implantation to the animal.

32. A method as claimed in claim 31, wherein the gestagen and the oestrogen are administered simultaneously.

33. A method as claimed in claim 31, wherein the gestagen and the oestrogen are administered separately.

34. A method as claimed in any one of claims 31 to 33, wherein the gestagen and the oestrogen are administered subcutaneously or intramuscularly.

35. A method as claimed in any one of claims 30 to 34, wherein the oestrogen and the gestagen are administered in the form of an oily solution.

36. A method as claimed in claim 35, wherein the oily solution contains sesame oil or castor oil as solvent.

37. A method as claimed in claim 35 or 36, wherein the oily solution also contains a diluent or a solubilizer.

38. A method as claimed in claim 37, wherein the diluent or solubilizer is benzyl benzoate.

39. A method as claimed in claim 35, wherein the oily solution contains a mixture of castor oil and benzyl benzoate as solvent.

40. A method as claimed in any one of claims 31 to 39, wherein the depot oestrogen is oestradiol oenanthate, oestradiol undecylate, oestradiol palmitate, oestradiol dibutyrate or oestradiol benzoate.

41. A method as claimed in any one of claims 31 to 40, wherein the gestagen is hydroxy-progesterone caproate, hydroxy - nor - progesterone caproate, medroxy-progesterone acetate or nor-ethyndrone caproate.

42. A method as claimed in any one of claims 31 to 40, wherein the gestagen is 17α - hydroxy - 19 - nor - progesterone, 6α - methyl - 17α - hydroxy - progesterone, 6 - methyl - 6 - dehydro - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 16α - methyl - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16α - methyl - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16β - methyl - 17α - hydroxy - progesterone, 6 - fluoro - 6 - dehydro - 16β - methyl - 17α - hydroxy - progesterone, 6, 16 - dimethyl - 6 - dehydro - 17α - hydroxy - progesterone, 6 - methyl - 6 - dehydro - 16 - methylene - 17α - hydroxy - progesterone, 6 - chloro - 6 - dehydro - 16 - methylene - 17α - hydroxy - progesterone, 1, 2 - methylene - 6 - chloro - 6 - dehydro - 17α - hydroxy - progesterone, 1, 2 - methylene - 6 - fluoro - 6 - dehydro - 17α - hydroxy - progesterone, 17α - ethynyl - testosterone, 17α - ethynyl - 19 - nor - testosterone, 17α - ethynyl - $\Delta^{5(10)}$ - oestren - 17β - ol - 3 - one, 17α - methyl - 19 - nor - testosterone, 17α - ethynyl - Δ^4 - oestrene - 3β, 17β - diol, 17α - ethynyl - Δ^4 - oestren - 17β - ol or a 17α - alkyl - Δ^4 - oestren - 17 - 17β - ol or a physiologically tolerable straight-chain or branched chain ester thereof.

43. A method as claimed in claim 42, wherein the ester is an acetate, valerate, butyrate, caproate, oenanthate or undecylate.

44. A method as claimed in any one of claims 31 to 40, wherein the gestagen is progesterone or a physiologically tolerable 3-enolester thereof.

45. A method as claimed in any one of claims 31 to 40, wherein the gestagen is 17α - ethynyl - 18 - homo - 19 - nor - testosterone.

46. A method as claimed in any one of claims 31 to 45, wherein the dose of oestrogen administered is capable of inducing a period of ovulation inhibition longer than that achieved by the oral administration of a daily dose of 0.05 mg of ethynyl - oestradiol.

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